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Treatment of Operation Wounds in Rats with Antibiotic-Coated Magnetic Nanoparticles

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Abstract

Research Article

Recent developments in drug technology have led to increasing interest in smart drug systems and systems that provide drug localisation in the area of infection. With the development of various nanoparticles, there have been new studies in this field related to the drug application routes and the effects of nanotechnology products. Drugs modified with nanoparticles have been found to be useful in transporting the drug to the target using systemic, oral, pulmonary, transdermal and other routes, in increasing the bioavailability capacity and protecting stability. The optic, fluorescent and magnetic properties of these nanoparticles are of particular benefit in the early determination of tumour cells and especially in the diagnosis and testing of various pathogenic and genetic diseases. Although studies related to the use of nanoparticles for treatment purposes are still very new, these types of studies have been published in literature in the last few years. The aim of this study was to evaluate the benefit of treatment with antibiotic-coated (enrofloxacin) magnetic nanoparticles added to the outside of a dressing and held on the wound area with the gravitational force of the magnets in an experimental rat model, where an operation wound had been infected with *Staphylococcus aureus*. Due to the magnetic areas of the magnets placed on the external wound region, the antibiotic-coated nanoparticles were maintained at a high concentration in the wound region, and by showing an effect with a single application without metabolisation in the liver, long-term adverse effects on the liver and kidneys were avoided.

INTRODUCTION

Infections developing in the operation wound and in the organs and areas in the surgical entry site within the first 30 days postoperatively are known as surgical site infections. Infections seen after a surgical intervention, despite sterilisation of the surgical instruments, and provision of asepsis and antisepsis preoperatively, intraoperatively and postoperatively, are the leading complications encountered in modern surgery[1].

In recent years in particular, the resistance formed in micro-organisms as a result of irrational use of antibiotics, and the more widespread use of biomaterials in the operations of elderly and immun suppressive patients have caused an increase in surgical site infections[1].

According to the National Nosocomial Infections Surveillance System (NNIS) data, the micro-organisms causing the most surgical site infections are coagulase positive and negative *Staphylococcus*, which are normally present in the microflora of the skin[1-3].

It is a well-known fact that in addition to the negative effects on wound healing of secondary infections formed in the operation region, micro-organisms mixed into the systemic circulation can cause a general infection table. When reasons such as these are considered, secondary infections in the operation area which require treatment are a signficant complication. In cases such as these, treatment is provided by systemic and local broad spectrum antibiotics. The disadvantage of local applications is that the drug administered is absorbed by surrounding tissues and expelled from the body in a short time, and thus there is a need for the antibiotics to be repeated. In systemic treatments, side-effects such as kidney and liver toxicity in particular, are frequently encountered problems[4].

As there are a great many treatment complications and side-effects of the drugs used, alternative treatment methods have been attempted by several researchers. Recent developments in drug technology have led to increasing interest in smart drug systems and systems that provide drug localisation in the area of infection. With the development of various nanoparticles, nanotechnology product research related to the drug application routes and effects has moved to this

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field[4].

The main problems are related to the general systemic distribution of therapeutic drugs, that the drug has no specificity directed to the area where the lesion is, the need to use high doses to reach the desired local concentration, non-specific toxicity and other side-effects of the agent used and systemic drug application. To overcome these problems, there has been focus on nanoparticles targetting the lesion or relevant area. As these types of agents can be directed to a limited area for treatment purposes, it may be possible to maintain strong drugs in a specified area[5].

Drug delivery systems based on the use of nano and micro particles have significant advantages such as the capability to target specific areas of the body, to reduce the amount of drug needed to reach a specific concentration around the target, and to minimise the severe side-effects of the concentration of the drug outside the target area[5,6]. The greatest problem encountered in the use of nanoparticles is maintaining a certain concentration of particles in the target tissue. Another potential benefit of the use of magnetic nanoparticles is that by being localised in a specific region of the body, they can be kept in that region until treatment is completed and can then be removed from the region at the end of treatment[7].

Magnetic nanoparticles designed for biomedical applications are generally biocompatible ferrite powders, which have been coated with an organic molecular shell with active pharmaceutical agents on the surface, functioning as magnetic nanoparticles. Physiologically, magnetic nanoparticles are well tolerated. For example, the toxicity of dextrane-magnetite cannot be measured according to the LD50 index. Iron oxides such as magnetic Fe_3O_4 are extremely resistant to oxidation and as there are no toxic properties, they are preferred in various applications[7-9].

For drugs used systemically to be able to reach a sufficient concentration in the infected region, the use of high doses and the need for repeated applications often cause unwanted effects in patients, and lead to several problems in the treatment process of surgical site infections, just as much as in other infections[7, 9]. By providing a concentration of the drug in the target tissue, smart drug systems aim to overcome these problems[7].

The aim of this study was to evaluate the results of operation wounds infected with *Staphylococcus aureus* created experimentally in rats, which were treated with antibiotic (enrofloxacin)-coated magnetic nanoparticles with much lower drug treatment doses applied subcutaneously, with the particles retained in the wound area by the gravitational force of magnets added to the dressing.

MATERIAL and METHOD

A total of 40, 4-month old, male, Wistar Albino rats, each weighing 210-230 gr were randomly separated into 5 groups of 8 rats. An area 5 x 5cm in the interscapular area was shaved.

For the synthesis of antibiotic-coated magnetic nanoparticles in the study, iron oxide nanoparticles of 30nm particle size were used (Sigma Aldrich -747467). They were treated with oleic acid for the antibiotic to be able to bind to the surface of the nanoparticles. To a 0.1 gr solid part, 6 ml oleic acid was added and mixed in a water bath at 80˚C for 30 mins. After terminating this mixing process, excess oleic acid was removed by adding 4ml deionised water to the nanoparticle-oleic acid complex. To obtain a single-layer magnetite nanoparticle coated with oleic acid, they were washed twice with 30 ml ethanol. The nanoparticles were dissolved by mixing the oleic acid-coated magnetite crystals in a solution of 30 mg enrofloxacin dissolved in 10 ml ethanol.

To obtain double-layer nanoparticles, the solution was mixed in a sonic mixer for 1 hour. After this process, the particles were expected to aggregate with 16x8x2 mm neodymium magnets to provide the drug targeting in the study. Following aggregation of sufficient particles with the magnets, the liquid was poured away and replaced with 20 ml PBS, the magnets were removed and the solution was made homogenous.

While the obtained solution was homogenous, a 1ml sample was taken and checked for whether or not the antibiotic coating method had been successful and to be able to understand the size of the obtained particles, analysis was performed with a scanning electron microscope (SEM).

The SEM analysis was performed in the Cumhuriyet University Advanced Technology Research and Application Centre laboratory using a TESCAN MIRA XMU3 device. For the measurements of the nanoparticles, a light force was applied at 10 kV at 14 units from a distance of approximately 10mm, and the measurements were taken with the vectoral post process system by taking images at different magnifications (x 50 k and x 200 k). Due to the high intensity, 15 kV was used for the tissue analyses and all the other data were left the same.

For the elemental analysis, the EDX analysis system was used, which has a $10mm^2$ surface area on the Inca model (Oxford Instruments) attached to the device. In this analysis, Fe separation was evaluated by analysing C, O, and Fe elements in the tissue. Peaks were collected with a spectrum program, and the regional analysis was completed with both mapping and the determination of the eV values of the peaks.

To be able to apply the antibiotic-coated, iron oxide nanoparticles to the rats, a simulation of an operation wound was made on the skin of all the rats. Under general anaesthesia (3 mg/kg xylazine + 90 mg/kg ketamine HCl ip), with the rats lying in the sternal position, a 1.5cm skin incision was made to the interscapular region. After injection to the incision line of 100µl of a solution containing *S. aureus* (BioBall-ATCC 6538) at a concentration of $1x10^8$ /ml (0.5 Mc Farland), the operation wound was sutured with 4-0 monofilament PGCL (Katsan) (Figure 1).

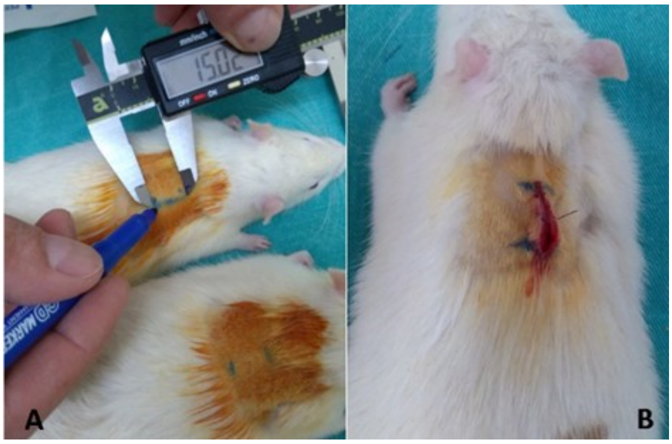

Figure 1. Creation of the operation wound in the rats. **A)** determining the length of the 1.5cm incision line with calipers. **B)** closing the created incision with 4-0 monofilament PGCL.

Before starting the application of the treatment procedure, Modified grading scale for inflammation[10] was applied to all the rats to make a macroscopic evaluation of inflammatory reactions. In the inflammation evaluation scale, findings were evaluated of the parameters of redness, swelling, and loss of function. Each parameter was scored from 0-2 points to determine the severity of the findings: 0= no finding, 1=moderate severity findings, and 2= severe findings (Table 1).

Table 1. Inflammation evaluation scale.

Rat	Group 1	Group 2	Group 3	Group 4	Group 5
1	2	2	2	2	2
2	2	2	2	1	2
3	1	1	2	2	2
4	2	1	1	2	2
5	2	2	2	2	2
6	2	2	2	2	2
7	2	1	2	2	2
8	2	2	2	2	2

Following the creation of infection, the rats were separated into 5 groups of 8 rats. Group 1 constituted the control group to which *S. aureus* was applied and no treatment was given. In Group 2, PBS-enrofloxacin was administered subcutaneously at a dose of 5mg/kg. In Group 3, iron oxide nanoparticles with no antibiotic coating were administered subcutaneously in a suspension of PBS at a dose of 5mg/kg. In Group 4, enrofloxacin-coated magnetic iron oxide nanoparticles were administered subcutaneously in a suspension of PBS at a dose of 2.5mg/kg, and in Group 5, at a dose of 5mg/kg. The neodyum magnets, 16 x 8 x 2mm in size, which were placed over the incision line in all the rats applied with nanoparticles were fixed with adhesive plaster bands (Figure 2).

Figure 2. Placement of the neodyum magnets over the incision line. **A)** the neodyum magnets used in the study **B)** The fixation dressing applied to the rats to be able to hold the magnets placed immediately over the incision line.

All the rats in all the groups were sacrificed appropriately on the 6th postoperative day. The interscapular region was excised en bloc to include the incision line and deep subcutaneous tissues. At the same time, tissue samples were taken from the spleen, kidney, liver and brain to examine whether there was any toxic effect of the nanoparticles on any internal organs. The tissues were placed in %10 formaldehyde then routinely processed and embedded paraffin. Sections were cut from the paraffin blocks of the tissues prepared for histopathological examination stained with hematoxylin and eosin (HE) for histopathological evaluation and these sections were fixed with adhesive carbon bands in 1 x1 mm layers. The tissue samples were examined with SEM for analysis and the presence of antibiotic-coated iron oxide nanoparticles in the area of application.

Statistical Analysis

Data obtained in the study were analysed using SPSS 14.01 software. The Kruskal Wallis test was applied to determine the significance of findings obtained in each variable. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The inflammation evaluation scale was applied to all the rats 3 days after the infection with *S. aureus*. The data of that scale are presented in Table 1.

After sacrifice of the rats on postoperative Day 6, the fixation bands were removed from Groups 3, 4 and 5. In Group 1, the control group, the wound lips were seen not to have completely closed in 6 of the 8 rats and oedema was determined in the area. In the other 2 rats, the wound line had completely closed and oedema was observed to have relatively recovered compared to the other animals (Figure 3A). In Group 2, the wound lips were closed in 7 rats and in 1, scatrix tissue was observed in placed of scab tissue in the wound line. In all 8 rats of Group 3, the wound line was determined to have closed, but the region was seen to be oedematous. In Group 4, the skin healing was completed with full closure in 7 of the 8 rats and in the other 1 rat, there was seen to be healing and most of the wound line was closed (Figure 3B). In Group 5, full wound healing was achieved in all the rats with no complications.

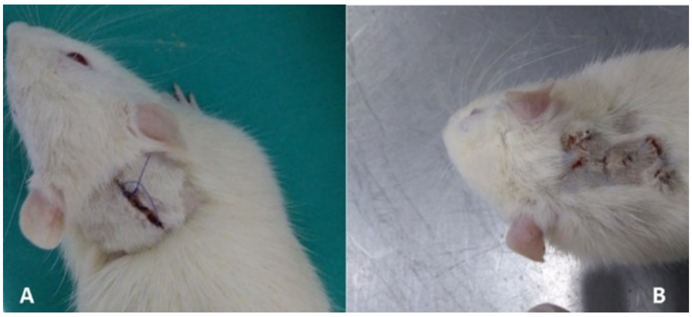

Figure 3. Macroscopic evaluation of the healing of the wound created in the rats. **A)** Swelling observed in the incision line of the control group. The wound line was determined not to have fully healed. **B)** On the postoperative 6th day, wound healing was completed in a rat of Group 4 and no infection was macroscopically observed in the area

At the end of the study, together with regeneration in the epidermis of the incision area, there was determined to be intense inflammatory infiltration of neutrophilic character in the dermis in the control group (Figure 4). The formation of connective tissue in the area was weak. In Group 2, given antibiotic only, full regeneration was observed in the epithelium of the incision line, and inflammation in the dermis was determined to be significantly reduced compared to the control group ($p<0.05$). The formation of connective tissue was significantly better than in the control group ($p<0.05$).

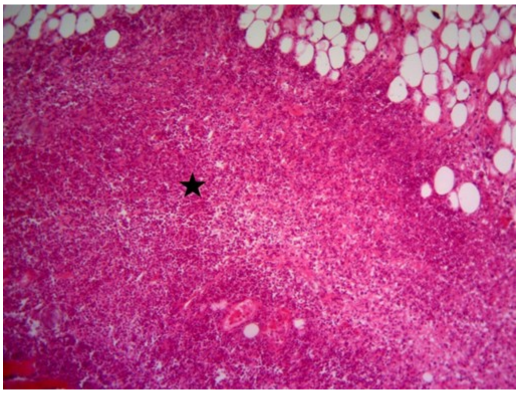

Figure 4. Histopathological examination of the control group, intense inflammatory infiltration of neutrophilic character was determined in the dermis (star) HE X10.

In Group 3, administered nanoparticles only, full regeneration was observed in the epithelium similar to that of the antibiotic group, mild inflammation was seen in the dermis and connective tissue formation was determined (epithelial tissue regeneration: $p>0.05$, inflammatory cell infiltration: $p>0.05$, connective tissue formation: $p>0.05$) (Figure 5). In Group 5, full regeneration was determined in the epidermis in the wound area in all the rats. Inflammation was seen to have fully recovered in the area and connective tissue formation was observed to have been completed (Figure 6).

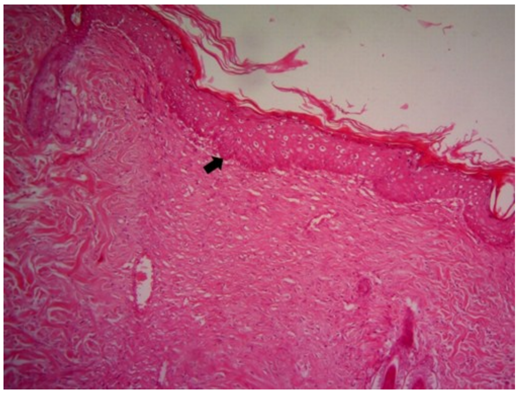

Figure 5. In Group 5, full regeneration was determined in the epidermis in the wound area (arrow). HE X10.

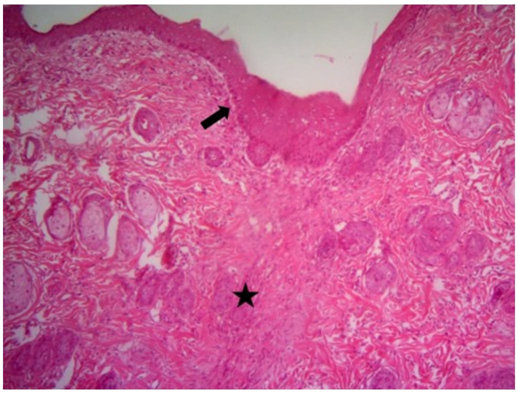

Figure 6. Group 4: slices taken from the cutaneous and subcutaneous region. Full epithelial regeneration was determined (arrow), inflammation had recovered (star) but this activity was weaker than in Group 5. HE X10.

The recovery occurring in this group was determined to be statistically significant in comparison with the control group (epithelial tissue regeneration: $p<0.05$, inflammatory cell infiltration: $p<0.05$, connective tissue formation: $p<0.05$). In Group 4, full epithelial regeneration occurred in all the animals, and inflammation had recovered (Figure 7). The formation of connective tissue was better than in the control group (epithelial tissue regeneration: $p<0.05$, inflammatory cell infiltration: $p<0.05$, connective tissue formation: $p<0.05$) but weaker than in Group 5 (epithelial tissue regeneration: $p<0.05$, inflammatory cell infiltration: $p<0.05$, connective tissue formation: $p<0.05$).

In the SEM examination, antibiotic-coated nitric oxide particles were seen to have regular distribution on the surface. Scattered agglomerations of nanometer-sized nuclei were seen and the reason for this was thought to be due to the advanced tendency of the electrostatic forces of colloidal suspensions to attract each other. In addition, the concentration and negative loading of an organic molecule, which is the apolar group, negatively affected the agglomeration characteristics (Figure 7A).

Measurements of the dispersed particles at x200 magnification were taken with examination of both the secondary electron and the back-scattered electron. While the secondary electron image gives a height difference to show the difference of the materials from the topography, the backscattered electron image makes it easier for the iron dense regions to be counted compared to the elemental density without being affected by the surface coating. In the statistical analysis made according to this, particle size was measured as 33 nm ± 3 nm. This showed that approximately 25nm particle size was of enrofloxacin, which is an organic molecule, sterically attached to the surfaces and the whole particle size was determined to have increased to 33nm in the surrounding form. Although standard deviation was not great, it is possible to mention antibiotic-coated iron oxide particles emerging at up to 40-50 nm because of the agglomeration of particles (Figure 7B).

The EDX mapping showing C, O, and Fe on the electron microscope image obtained with Au coating on the slide following tissue fixation is shown in Figure 8. While C and O peaks, originating from organic material consistent with tissue, were active in certain locations, Fe element was seen in the tissue walls and within the tissue. It is possible to say that this was due to the antibiotic treatment being held in the area that was the source of the magnetism. This finding was seen to be in parallel with the histopathological findings.

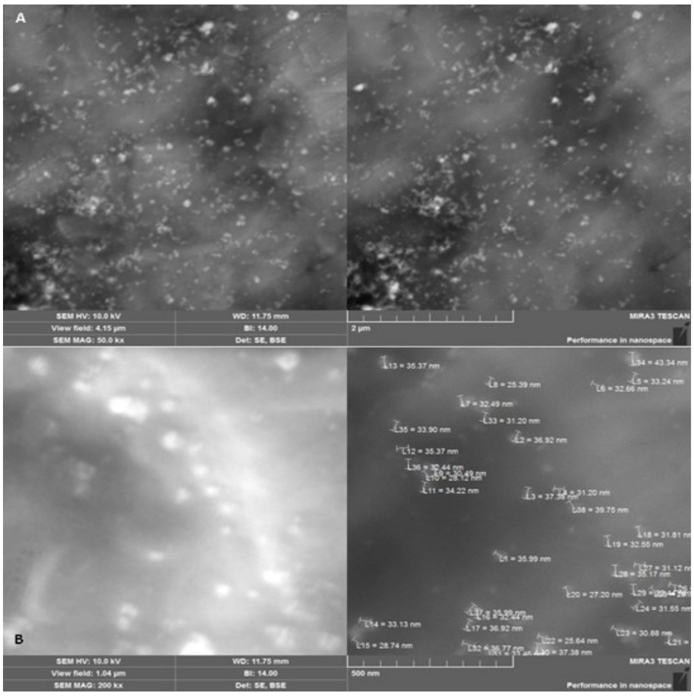

Figure 7. SEM image of dispersed particles at x 200k magnification **A)** SEM image of antibiotic-coated iron oxide nanoparticles distribution **B)** particle size.

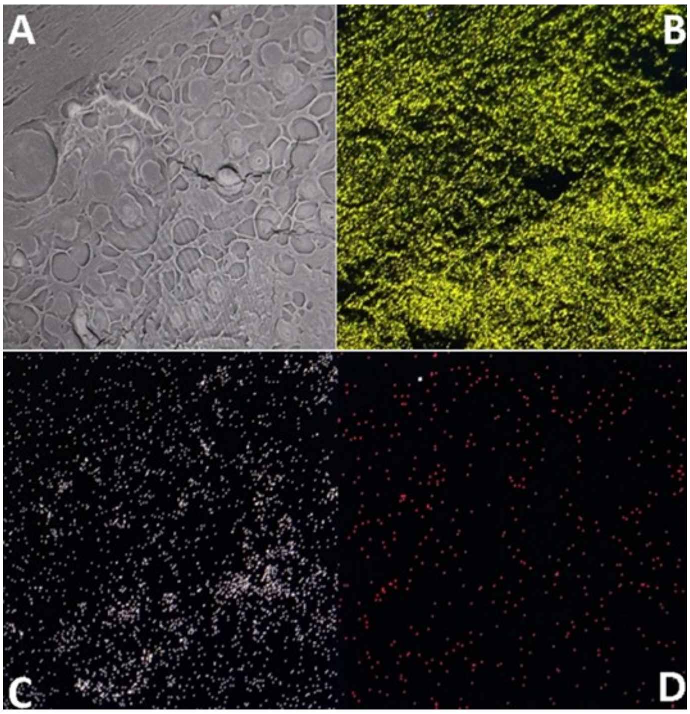

Figure 8. EDX mapping showing C, O, and Fe on the SEM image obtained with Au coating on the slide following tissue fixation **A)** SEM image of tissue in the operation area, **B)** carbon **C)** oxygen **D)** iron elements determined in the area as a result of EDX mapping.

DISCUSSION

The idea of magnetic micro and nano particles to transport therapeutic drugs by targetting specific regions of the body goes back as far as the 1970s. For targeting purposes, the drug-loaded magnetic particles are injected into the subject by intravenous or intra-arterial injection[11] and the application of external magnetism ensures that the drug reaches the target. In a study of tumours by Widder et al, an intra-arterial injection close to the tumour area was used to increase the efficacy of magnetic targetting. In the comparisons made, it was reported that the targetting of this application was 200-fold more effective than an intravenous injection. Then in studies using animal models such as pigs, rabbits and rats, success was reported in cytotoxic drug distribution and tumour remission. By modifying this technique, Kubo et al, placed permanent magnets in the area of a solid osteosarcoma in hamsters, and transmitted cytotoxic components through magnetic liposomes. In comparison to normal (non-magnetic) intravenous delivery, there was seen to be a 4-fold increase in the efficacy of cytotoxic drug delivery with this method[5].

In the current study, an operation wound was simulated. The interscapular area was selected as the incision area as the rats would not be able to reach there. A 1.5cm long incision was made, then the area was infected with *S. aureus* and sutured with 4/0 monofilament suture thread. After infection was formed, to be able to obtain maximum efficacy in the magnetic targetting, iron oxide nanoparticles not coated with antibiotics were injected subcutaneously at a dose of 5 mg/kg to the animals in Group 3, and enrofloxacin-coated iron oxide magnetic nanoparticles were injected subcutaneously at 2.5mg/kg to Group 4 and at 5mg/kg to Group 5. The magnets were placed imediately over the wound line and fixed with bands to close the area.

On the postoperative 6th day, the suture line was observed to have completely closed in 7 rats of Group 4 and all the rats of Group 5. The results obtained in the current study were in parallel with those of previous tumour studies and consistent with the data in literature. In addition, epithelial regeneration, formation of connective tissue and complete recovery of inflammation were observed in Group 5. Similar healing was determined in Group 4, with less connective formation than in Group 5. The healing parameters of these two groups were seen to be statistically significantly better than those of the control group and the other groups. Therefore, these results suggest that the administration of antibiotic-coated magnetic nanoparticles contributed far more to the wound healiing process than nanoparticles only or antibiotic only.

When the SEM and histological evaluation data are taken into consideration, success was provided by magnetic targetting. In the light of information in literature, it can be considered that the drug-nanoparticle complex applied to the venous or arterial circulation has a lower potential and retention rate in the area than subcutaneous delivery, where it is captured by magnetism. Therefore, by applying magnetism from outside the area, when particles are injected subcutaneously there is less particle loss, and it is aimed to retain the particles around the incision line as far as possible. In the findings obtained from EDX mapping, the presence of iron oxide particles was proven within and over cells in the healing line, and when the retention of particles in the area and the success of wound healing are taken into consideration, it can be concluded that more effective results can be obtained from magnetic targetting of particles applied subcutaneously.

The majority of micro-organisms causing infections after surgical interventions are found in the natural flora of the skin, mucous membranes or intestines. In the formation of surgical site infection, the degree of contamination of the operation wound is a significant factor. The use of antibiotics is extremely important in the prevention of surgical site infections[12]. In animal studies, it has been shown that antibiotic use can prevent or reduce infection in the operation area[13]. Antibacterial activity has the effect of preventing the development of or killing micro-organisms without creating a toxic effect on surrounding tissues[9]. The selection of the appropriate antibiotic, correct dosage and regular use are very important[12].

In a previous study, infection in the operation area was observed to be increased 2-fold in patients not administered postoperative antibiotherapy. *S. aureus* has been shown to be the leading bacteria causing the most surgical site infections. Antibiotic treatment should be directed at these types of micro-organisms that have probably contaminated the operation wound[14]. However, due to irrational antibiotic use, bacterial resistance to antibacterial agents has become a major problem. Antibiotic treatment underlies the resistance formed to antibacterial agents and this leads to the formation of fatal resistance. Therefore, because of the bacterial resistance process developing against several antibiotic agents, the treatment of infectious diseases continues to be a major problem worldwide. Moreover, not only being multi-drug-resistant, but also the potential side-effects of conventional antimicrobial agents constitute a problem. Drug resistance usually arises from antibiotic use at high doses with tolerable toxicity. This has led to the need for the development of alternative treatment methods for bacterial patients. Of these, nano-scale materials have come to be used as rescue antibacterial agents. In both experimental animal models and in vitro environments, various types of antimicrobial nanoparticles and nano-sized carriers which help to direct antibiotics have been proven to effectively treat infectious diseases that have developed antibiotic resistance[9].

In this study, operation wounds infected with *S. aureus* were subcutaneously injected with enrofloxacin-coated magnetic iron oxide nanoparticles, which were held in the wound area with the magnetism applied from outside. In the clinical and histopathological evaluations made at the end of 6 days, no inflammation or infection was present in the rats of these groups. It was concluded that the successful healing achieved in Groups 4 and 5 was due to the application of a single dose held in the operation area with the external magnetism of the magnetic particles, and thus continued effectiveness of the antibiotic-coated nanoparticles was obtained without the nanoparticles entering the circulation and avoiding the need for repeated doses of antibiotics, and thus the infection was treated. The potential systemic side-effects were avoided of the traditionally repeated doses of antibiotherapy applied to patients in the postoperative period. Furthermore, no findings of degeneration or toxicity caused by particles were determined in the histopathological examination of the samples of internal organs taken from the rats.

The primary aim of wound treatment is to obtain rapid wound closure and the formation of a functional and aesthetically satisfactory scar[15].

The operation wounds closed rapidly without any problems in all the groups where antibiotic was used. In the clinical examination, no findings of pain or inflammation were observed. As the operation area was completely closed on the 6th postoperative day, especially in Groups 4 and 5, it was concluded that the antibiotic held in the area with magnetism was useful in completing epithelialisation without any problems by overcoming complications that could be experienced associated with infection during the healing process.

The most important disadvantage of nanoparticles and antibacterial drugs is that they are not successful in interventions against bacteria such as *S. aureus* that have the capability to produce a biofilm. A biofilm is the aggregation of complex bacteria on a solid surface held together through matrix secretion. It is known to be an important problem because biofilm formation protects against pathogenic bacteria, antibiotics and other antimicrobial agents. This is the leading cause of chronic infections[9].

S. aureus was used in the current study as it is one of the bacteria with the ability to produce biofilm. After the creation of infection, enrofloxacin was selected as the antibiotic treatment in the rats at a pure treatment dose and at a lower treatment dose bound to the nanoparticles. From the results obtained of the healing observed in the rats in Groups 4 and 5, it was concluded that better healing was achieved than in Group 2 where pure enrofloxacin was used. In the treatment of infection created by *S. aureus*, which has the ability to form a biofilm layer, the nanoparticle-enrofloxacin complex was seen to be successful. These results were consistent with information in literature.

Magnetic nanoparticles are an extremely new topic in veterinary medicine. Together with the developments in drug technology, the systems known as smart drug systems which provide localisation of the drug in the infection area, have recently attracted great attention. As a result of research related to drug delivery routes and effects, nanoparticles are now considered an alternative method in various treatments. Positive results have been seen to have been obtained using various delivery routes for combinations of drugs with these particles in increasing the benefit of the drug and targeting the drug to a specific area.

With the benefit of the optic, fluorescent and magnetic properties of nanoparticles, testing and diagnosis of various diseases can be achieved, and the early determination of tumour cells and their elimination by cytotoxic agents targetting tumoural tissue and cells. Studies related to the use of nanoparticles for treatment purposes are still very new.

In this study, operation wounds infected with *S. aureus* created experimentally in rats were treated with antibiotic-coated (enrofloxacin) magnetic nanoparticles with much lower drug treatment doses applied subcutaneously, with the particles retained in the wound area by the gravitational force of magnets added to the dressing.

Due to the magnetic field of the magnets placed over the wound area from the outside, the antibiotic-coated nanoparticles were retained at a high concentration in the wound area, and by having an effect with a single dose without metabolisation in the liver, the antibiotics were in the body for a long time, and adverse effects on the liver and kidneys were avoided.

In conclusion, the results of this experimental study demonstrated that antibiotic-coated magnetic iron oxide nanoparticles treated the infection in infected wounds and could be considered as an extremely useful alternative treatment method to traditionally applied antibiotic treatments.

Ethical Approval

This study was accepted by Sivas Cumhuriyet University Ethical Committee of Animal Experiment with confirmation number: 65202830-050.04.04-81

Conflicts of Interest

The authors declare that they have no conflict of interests.

Financial disclosure

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